Clinical trial results:
A randomized, double-blind, double-dummy, multi-center study to assess safety and efficacy of BAY- 948862 in subjects with emergency presentation at the hospital because of worsening chronic heart failure with left ventricular systolic dysfunction and either type 2 diabetes mellitus with or without chronic kidney disease or moderate chronic kidney disease alone versus eplerenone

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-002627-15
Trial protocol	FI AT SE LT DE HU CZ NO NL PT DK IT ES BG GR PL
Global end of trial date	22 January 2015

Results information

Result version number	v1
This version publication date	09 July 2016
First version publication date	09 July 2016

Trial information

Trial identification

Sponsor protocol code	BAY94-8862/14564

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01807221
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to investigate efficacy (percentage of subjects with a relative decrease in N-terminal pro-hormone B-type natriuretic peptide [NT-proBNP] of more than 30 percent [%] from baseline to Day 90 [Day 90+/-2]) and safety of different oral doses of finerenone given once daily OD).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 117
Country: Number of subjects enrolled	Portugal: 26
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	Sweden: 29
Country: Number of subjects enrolled	Austria: 22
Country: Number of subjects enrolled	Bulgaria: 128
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Denmark: 31
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 73
Country: Number of subjects enrolled	Greece: 73

Country: Number of subjects enrolled	Hungary: 144
Country: Number of subjects enrolled	Italy: 67
Country: Number of subjects enrolled	Lithuania: 80
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Taiwan: 32
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 58
Country: Number of subjects enrolled	Israel: 153
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	Korea, Republic of: 21
Worldwide total number of subjects	1286
EEA total number of subjects	943

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	349
From 65 to 84 years	856
85 years and over	81

Subject disposition

Recruitment

Recruitment details:

Study was conducted in 168 study centers in 25 countries worldwide, from 17 June 2013 (first subject first visit) to 09 December 2014 (last subject last visit).

Pre-assignment

Screening details:

Out of 1286 enrolled subjects, 1066 subjects were randomized and 220 subjects were excluded due to screening failures.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Eplerenone (INSPRA®)

Arm description:

Eplerenone 25 milligram (mg) capsule every other day (EOD), on Day 1, Day 3, Day 5, etc, along with placebo capsule (matched to Eplerenone capsule) on Day 2, Day 4, Day 6, etc., and placebo tablet (matched to Finerenone tablet) once daily (OD).The dose could be increased to 25 mg OD at Day 30 and to 50 mg OD at Day 60 (or 25 mg OD if no up-titration occurred on Day 30) if both up-titration steps were performed. Treatment duration was for 90 days.

Arm type	Experimental
Investigational medicinal product name	Eplerenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 25mg of Eplerenone EOD up to Day 30. Potential up-titration to 25 mg OD after 30 days and 50 mg OD after 60 days.

Investigational medicinal product name	Placebo tablet (matched to Finerenone tablet)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of placebo tablet (matched to Finerenone tablet) during any intervention period of the study.

Investigational medicinal product name	Placebo capsule (matched to Eplerenone capsule)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of placebo capsule (matched to Eplerenone capsule) during any intervention period of the study.

Arm title	Finerenone (BAY94-8862) 2.5-5 mg OD

Arm description:

Finerenone 2.5 mg immediate-release (IR) tablets OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 5 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Arm type	Experimental
Investigational medicinal product name	Finerenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2.5 mg finerenone tablet OD in the morning, with possible up-titration to 5 mg OD.

Investigational medicinal product name	Placebo capsule (matched to Eplerenone capsule)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of placebo capsule (matched to Eplerenone capsule) during any intervention period of the study.

Arm title	Finerenone (BAY94-8862) 5-10 mg OD

Arm description:

Finerenone 5 mg IR tablets OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 10 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Arm type	Experimental
Investigational medicinal product name	Finerenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5 mg finerenone tablet OD in the morning, with possible up-titration to 10 mg OD.

Investigational medicinal product name	Placebo capsule (matched to Eplerenone capsule)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of placebo capsule (matched to Eplerenone capsule) during any intervention period of the study.

Arm title	Finerenone (BAY94-8862) 7.5-15 mg OD

Arm description:

Finerenone 7.5 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 15 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Arm type	Experimental
Investigational medicinal product name	Finerenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 7.5 mg finerenone tablet OD in the morning, with possible up-titration to 15 mg OD.

Investigational medicinal product name	Placebo capsule (matched to Eplerenone capsule)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of placebo capsule (matched to Eplerenone capsule) during any intervention period of the study.

Arm title	Finerenone (BAY94-8862) 10-20 mg OD

Arm description:

Finerenone 10 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Arm type	Experimental
Investigational medicinal product name	Finerenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 10 mg finerenone tablet OD in the morning, with possible up-titration to 20 mg OD.

Investigational medicinal product name	Placebo capsule (matched to Eplerenone capsule)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of placebo capsule (matched to Eplerenone capsule) during any intervention period of the study.

Arm title	Finerenone (BAY94-8862) 15-20 mg OD

Arm description:

Finerenone 15 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Arm type	Experimental
Investigational medicinal product name	Finerenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 15 mg finerenone tablet OD in the morning, with possible up-titration to 20 mg OD.

Investigational medicinal product name	Placebo capsule (matched to Eplerenone capsule)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of placebo capsule (matched to Eplerenone capsule) during any intervention period of the study.

Number of subjects in period 1[1]	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD
Started	224	173	165
Completed	144	121	122
Not completed	80	52	43
Consent withdrawn by subject	33	15	8
Physician decision	2	1	-
Logistical difficulties	-	1	-
Protocol violation	-	2	1
Death	7	9	4
Adverse event	33	22	26
Non-compliance	1	2	-
Sponsor decision	2	-	1
Lost to follow-up	1	-	2
Progressive disease	1	-	1

Number of subjects in period 1[1]	Finerenone (BAY94-8862) 7.5-15 mg OD	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD
Started	169	170	165
Completed	123	134	124
Not completed	46	36	41
Consent withdrawn by subject	14	16	13
Physician decision	-	-	-
Logistical difficulties	-	1	-
Protocol violation	2	-	1
Death	2	1	6
Adverse event	25	18	21
Non-compliance	1	-	-
Sponsor decision	1	-	-
Lost to follow-up	1	-	-
Progressive disease	-	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Eplerenone (INSPRA®)
Reporting group description:	
Eplerenone 25 milligram (mg) capsule every other day (EOD), on Day 1, Day 3, Day 5, etc, along with placebo capsule (matched to Eplerenone capsule) on Day 2, Day 4, Day 6, etc., and placebo tablet (matched to Finerenone tablet) once daily (OD).The dose could be increased to 25 mg OD at Day 30 and to 50 mg OD at Day 60 (or 25 mg OD if no up-titration occurred on Day 30) if both up-titration steps were performed. Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 2.5-5 mg OD
Reporting group description:	
Finerenone 2.5 mg immediate-release (IR) tablets OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 5 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 5-10 mg OD
Reporting group description:	
Finerenone 5 mg IR tablets OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 10 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 7.5-15 mg OD
Reporting group description:	
Finerenone 7.5 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 15 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 10-20 mg OD
Reporting group description:	
Finerenone 10 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 15-20 mg OD
Reporting group description:	
Finerenone 15 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	

Reporting group values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD
Number of subjects	224	173	165
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	72.38	72.53	71.81
standard deviation	± 9.92	± 9.74	± 10.55
Gender Categorical Units: Subjects			
Female	51	37	38
Male	173	136	127

Reporting group values	Finerenone (BAY94-8862) 7.5-15 mg OD	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD

Number of subjects	169	170	165
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	69.27	71.27	69.2
standard deviation	± 9.83	± 10.27	± 10.15
Gender Categorical Units: Subjects			
Female	44	41	31
Male	125	129	134

Reporting group values	Total		
Number of subjects	1066		
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	242		
Male	824		

End points

End points reporting groups

Reporting group title	Eplerenone (INSPRA®)
Reporting group description:	
Eplerenone 25 milligram (mg) capsule every other day (EOD), on Day 1, Day 3, Day 5, etc, along with placebo capsule (matched to Eplerenone capsule) on Day 2, Day 4, Day 6, etc., and placebo tablet (matched to Finerenone tablet) once daily (OD).The dose could be increased to 25 mg OD at Day 30 and to 50 mg OD at Day 60 (or 25 mg OD if no up-titration occurred on Day 30) if both up-titration steps were performed. Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 2.5-5 mg OD
Reporting group description:	
Finerenone 2.5 mg immediate-release (IR) tablets OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 5 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 5-10 mg OD
Reporting group description:	
Finerenone 5 mg IR tablets OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 10 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 7.5-15 mg OD
Reporting group description:	
Finerenone 7.5 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 15 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 10-20 mg OD
Reporting group description:	
Finerenone 10 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Reporting group title	Finerenone (BAY94-8862) 15-20 mg OD
Reporting group description:	
Finerenone 15 mg IR tablet OD and placebo capsule (matched to Eplerenone capsule) OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
(N=1055) All randomized subjects who took at least one dose of study drug and with data after beginning of treatment.	
Subject analysis set title	Full Analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
(N=1002) All subjects of the SAF who had baseline and at least one post-baseline NT-proBNP value or who died or experienced permanent (≥5 consecutive days) withdrawal of study drug after cardiovascular (CV) hospitalization or after emergency presentation for WCHF.	
Subject analysis set title	Per-protocol analysis set (N=PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
(654) All subjects of the FAS who had valid NT-proBNP data at Day 60 (Day 60±2) or later and had no major protocol deviations.	
Subject analysis set title	Pharmacokinetic analysis set (N=PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
(786) All finerenone-treated subjects with at least one valid finerenone plasma concentration and without any protocol deviation that would interfere with the evaluation of the PK data.	

Primary: Percentage of Subjects With a Relative Decrease in NTproBNP of More Than 30 % From Baseline to Day 90 (Day 90±2)

End point title	Percentage of Subjects With a Relative Decrease in NTproBNP of More Than 30 % From Baseline to Day 90 (Day 90±2)

End point description:

N-terminal pro-B type natriuretic peptide (NT-proBNP) levels in the blood are used for screening, diagnosis of acute and chronic heart failure (CHF) and may be useful to establish prognosis in heart failure.

End point type	Primary

End point timeframe:

At Day 90 (Day 90±2)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207[1]	162[2]	157[3]	158[4]
Units: Percentage of Subjects				
number (confidence interval 90%)	37.2 (31.6 to 43.1)	30.9 (24.9 to 37.4)	32.5 (26.3 to 39.2)	37.3 (30.9 to 44.1)

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[5]	158[6]		
Units: Percentage of Subjects				
number (confidence interval 90%)	38.8 (32.3 to 45.5)	34.2 (27.9 to 40.9)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimates and two-sided 90% confidence intervals are provided for each treatment group and for the treatment differences πBi - πC. Clopper-Pearson confidence intervals were calculated for each treatment group, while for treatment differences the exact unconditional confidence limits were calculated.

Comparison groups	Eplerenone (INSPRA®) v Finerenone (BAY94-8862) 2.5-5 mg OD

Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8771
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-6.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.9
upper limit	2.3

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Estimates and two-sided 90% confidence intervals are provided for each treatment group and for the treatment differences πBi - πC. Clopper-Pearson confidence intervals were calculated for each treatment group, while for treatment differences the exact unconditional confidence limits were calculated.

Comparison groups	Eplerenone (INSPRA®) v Finerenone (BAY94-8862) 5-10 mg OD
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7945
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-4.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.4
upper limit	4

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Estimates and two-sided 90% confidence intervals are provided for each treatment group and for the treatment differences πBi - πC. Clopper-Pearsonconfidence intervals were calculated for each treatment group, while for treatment differences the exact unconditional confidence limits were calculated.

Comparison groups	Eplerenone (INSPRA®) v Finerenone (BAY94-8862) 7.5-15 mg OD
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	0.1

Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.5
upper limit	8.8

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Estimates and two-sided 90% confidence intervals are provided for each treatment group and for the treatment differences πBi - πC. Clopper-Pearsonconfidence intervals were calculated for each treatment group, while for treatment differences the exact unconditional confidence limits were calculated.

Comparison groups	Eplerenone (INSPRA®) v Finerenone (BAY94-8862) 10-20 mg OD
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4225
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.1
upper limit	10.2

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Estimates and two-sided 90% confidence intervals are provided for each treatment group and for the treatment differences πBi - πC. Clopper-Pearson confidence intervals were calculated for each treatment group, while for treatment differences the exact unconditional confidence limits were calculated.

Comparison groups	Eplerenone (INSPRA®) v Finerenone (BAY94-8862) 15-20 mg OD
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6865
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.7
upper limit	5.7

Secondary: Number of Subjects With Death due to any Cause

End point title	Number of Subjects With Death due to any Cause

End point description:

Death due to any cause include cardiovascular (CV) death and Non-CV death. Non-CV death was classified by 2 subcategories: non-malignant causes and malignant causes. End of treatment is defined as the last study drug intake + 3 days.

End point type	Secondary

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207[7]	162[8]	157[9]	158[10]
Units: Subjects				
Day 30	6	5	1	1
Day 60	7	7	3	2
Day 90	9	10	4	4
End of Treatment	9	10	4	5
End of Follow-up	15	16	7	11

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

[10] - FAS

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[11]	158[12]		
Units: Subjects				
Day 30	0	2		
Day 60	0	4		
Day 90	1	5		
End of Treatment	1	5		
End of Follow-up	2	8		

Notes:

[11] - FAS

[12] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Cardiovascular Hospitalization

End point title	Number of Subjects With Cardiovascular Hospitalization

End point description:

Hospitalizations were defined as any unplanned admission to hospital, i.e. completion of hospital admission procedures and one overnight [i.e. date change] stay or until the death of subject occurred.

Hospitalizations and deaths were classified by 2 primary categories: CV and non-CV. The pre-specified subcategories for CV hospitalizations were as follows: 1. Worsening heart failure, 2.Acute myocardial infarction, 3. Arrhythmia, 4.Transient ischemic attack and stroke, 5. Other CV hospitalizations. End of treatment is defined as the last study drug intake + 3 days.

End point type	Secondary

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207[13]	162[14]	157[15]	158[16]
Units: Subjects				
Day 30	28	23	14	8
Day 60	43	33	23	21
Day 90	45	35	26	29
End of Treatment	46	35	26	29
End of Follow-up	56	43	38	36

Notes:

[13] - FAS

[14] - FAS

[15] - FAS

[16] - FAS

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[17]	158[18]		
Units: Subjects				
Day 30	7	15		
Day 60	15	23		
Day 90	22	28		
End of Treatment	22	29		
End of Follow-up	27	34		

Notes:

[17] - FAS

[18] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Emergency Presentations for Worsening Chronic Heart Failure (WCHF)

End point title	Number of Subjects With Emergency Presentations for Worsening Chronic Heart Failure (WCHF)

End point description:

Emergency presentations for WCHF were defined as newly developing signs and symptoms of WCHF after start of treatment with study drug, requiring an additional emergency presentation to hospital and IV treatment with diuretics and/or positive inotropic agents. End of treatment is defined as the last study drug intake + 3 days.

End point type	Secondary

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207[19]	162[20]	157[21]	158[22]
Units: Subjects				
Day 30	21	19	12	9
Day 60	35	30	20	17
Day 90	37	32	22	24
End of Treatment	37	32	22	24
End of Follow-up	47	40	30	30

Notes:

[19] - FAS

[20] - FAS

[21] - FAS

[22] - FAS

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[23]	158[24]		
Units: Subjects				
Day 30	7	15		
Day 60	14	22		
Day 90	18	28		
End of Treatment	18	30		
End of Follow-up	26	34		

Notes:

[23] - FAS

[24] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Dose on B-type natriuretic peptide (BNP)

End point title	Effect of Dose on B-type natriuretic peptide (BNP)

End point description:

B-type natriuretic peptide (BNP) levels in the blood are used for screening, diagnosis of acute chronic heart failure (CHF) and may be useful to establish prognosis in heart failure.

End point type	Secondary

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	203[25]	156[26]	151[27]	156[28]
Units: picogram per milliliter (pg/mL)				
geometric mean (standard deviation)				
Baseline (n=203, 156, 151, 156, 158, 155)	594.29 (± 2.601)	677.906 (± 2.637)	574.245 (± 2.543)	570.776 (± 2.741)
Day 30 (n=176, 136, 136, 141, 139, 133)	0.925 (± 2.02)	0.944 (± 1.952)	0.878 (± 1.713)	0.832 (± 1.959)
Day 60 (n=148, 130, 128, 125, 133, 128)	0.783 (± 2.194)	0.864 (± 2.139)	0.854 (± 1.854)	0.79 (± 2.179)
Day 90 (n=141, 119, 122, 119, 127, 120)	0.723 (± 2.202)	0.813 (± 2.412)	0.839 (± 1.93)	0.719 (± 2.204)
Last on-Treatment (n=180,145,139,145,143,140)	0.757 (± 2.231)	0.84 (± 2.349)	0.853 (± 1.931)	0.732 (± 2.185)
Premature discontinuation (n=33,23,22,19,21,22)	0.896 (± 0.896)	1.104 (± 2.15)	1.006 (± 2.422)	0.884 (± 1.973)
Follow-up (n=165,128,136,126,143,136)	0.795 (± 2.232)	0.815 (± 2.388)	0.886 (± 2.199)	0.726 (± 2.397)

Notes:

[25] - FAS

[26] - FAS

[27] - FAS

[28] - FAS

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158[29]	155[30]		
Units: picogram per milliliter (pg/mL)				
geometric mean (standard deviation)				
Baseline (n=203, 156, 151, 156, 158, 155)	606.08 (± 2.598)	552.032 (± 2.698)		
Day 30 (n=176, 136, 136, 141, 139, 133)	0.852 (± 1.901)	0.879 (± 1.968)		
Day 60 (n=148, 130, 128, 125, 133, 128)	0.711 (± 2.116)	0.824 (± 2.142)		
Day 90 (n=141, 119, 122, 119, 127, 120)	0.706 (± 2.34)	0.771 (± 2.197)		
Last on-Treatment (n=180,145,139,145,143,140)	0.702 (± 2.28)	0.777 (± 2.173)		
Premature discontinuation (n=33,23,22,19,21,22)	0.848 (± 2.218)	1.044 (± 2.174)		
Follow-up (n=165,128,136,126,143,136)	0.729 (± 2.487)	0.852 (± 2.169)		

Notes:

[29] - FAS

[30] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Dose on N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)

End point title	Effect of Dose on N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)

End point description:

N-terminal pro-B type natriuretic peptide (NT-proBNP) levels in the blood are used for screening, diagnosis of acute chronic heart failure (CHF) and may be useful to establish prognosis in heart failure.

End point type	Secondary

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207[31]	162[32]	157[33]	158[34]
Units: pg/mL				
geometric mean (standard deviation)				
Baseline (n=207, 162, 157, 158, 160, 158)	4730.17 (± 2.938)	4793.43 (± 3.084)	4184.631 (± 3.093)	3776.859 (± 3.395)
Day 30 (n=177, 137, 139, 145, 141, 136)	0.883 (± 2.458)	0.98 (± 2.158)	0.874 (± 2.14)	0.888 (± 2.123)
Day 60 (n=153, 131, 127, 125, 137, 130)	0.749 (± 2.73)	0.822 (± 2.423)	0.814 (± 2.178)	0.81 (± 2.268)
Day 90 (n=142, 119, 120, 118, 129, 121)	0.688 (± 2.59)	0.789 (± 2.661)	0.765 (± 2.214)	0.783 (± 2.454)
Last on-Treatment (n=180,145,139,146,143,141)	0.755 (± 2.522)	0.841 (± 2.552)	0.797 (± 2.215)	0.81 (± 2.35)
Premature discontinuation (n= 36,23,24,21,22,25)	0.948 (± 2.684)	1.369 (± 2.087)	1.267 (± 2.261)	0.927 (± 1.864)
Follow-up (n=165,130,139,131,144,137)	0.747 (± 2.616)	0.747 (± 2.741)	0.887 (± 2.604)	0.809 (± 2.647)

Notes:

[31] - FAS

[32] - FAS

[33] - FAS

[34] - FAS

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[35]	158[36]		
Units: pg/mL				
geometric mean (standard deviation)				
Baseline (n=207, 162, 157, 158, 160, 158)	4163.898 (± 2.734)	3791.677 (± 3.013)		
Day 30 (n=177, 137, 139, 145, 141, 136)	0.822 (± 2.217)	0.921 (± 2.136)		
Day 60 (n=153, 131, 127, 125, 137, 130)	0.748 (± 2.496)	0.829 (± 2.288)		

Day 90 (n=142, 119, 120, 118, 129, 121)	0.728 (± 2.795)	0.771 (± 2.471)		
Last on-Treatment (n=180,145,139,146,143,141)	0.735 (± 2.717)	0.771 (± 2.479)		
Premature discontinuation (n= 36,23,24,21,22,25)	1.133 (± 2.981)	0.965 (± 2.352)		
Follow-up (n=165,130,139,131,144,137)	0.746 (± 2.472)	0.849 (± 2.348)		

Notes:

[35] - FAS

[36] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-Related Quality of Life to Day 30 (Day 30±2) and Day 90 (Day 90±2) Assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ)

End point title	Change From Baseline in Health-Related Quality of Life to Day 30 (Day 30±2) and Day 90 (Day 90±2) Assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ)

End point description:

The KCCQ was the leading health related quality of life measure for subjects with CHF. KCCQ was a 23 item questionnaire that independently measures the impact of subjects HF, or its treatment, on 7 distinct domains: self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. KCCQ clinical summary score is a composite assessment of physical limitations and total symptom scores. Results from the total symptom summary score are presented. Scores are transformed to a range of 0-100, in which higher scores reflect better health status. In the below table, categorical data represents change from baseline data at respective time points.

End point type	Secondary

End point timeframe:

Baseline, Day 30, Day 90

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	203	161	156	158
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline (n= 203, 161, 156, 158, 160, 157)	43.7 (± 23)	42.8 (± 22.6)	45.4 (± 24)	42.1 (± 23.2)
Day 30 (n=177, 141, 137, 145, 141, 141)	20.5 (± 26.2)	18.2 (± 22.7)	19.3 (± 26.5)	23 (± 24.4)
Day 90 (n=141, 118, 121, 118, 129, 119)	24.3 (± 27.6)	21.3 (± 27.2)	24.5 (± 27)	29.3 (± 28.6)

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	157		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline (n= 203, 161, 156, 158, 160, 157)	42.3 (± 23.7)	43.2 (± 22.5)		
Day 30 (n=177, 141, 137, 145, 141, 141)	24.9 (± 22.9)	20.6 (± 27)		
Day 90 (n=141, 118, 121, 118, 129, 119)	28.3 (± 23.8)	22.2 (± 30.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline With Transitions From Baseline With Respect to EuroQol Group 5-Dimension, 3-Level Questionnaire (EQ-5D-3L)

End point title	Change from Baseline With Transitions From Baseline With Respect to EuroQol Group 5-Dimension, 3-Level Questionnaire (EQ-5D-3L)

End point description:

EQ-5D-3L: participant rated questionnaire to assess health-related quality of life. It consists of EQ-5D descriptive system and EQ-5D Visual Analog Scale (VAS). EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems (1), some problems (2), and extreme problems (3). The 5 dimensional 3-level systems are converted into a single index utility score. Values for theoretically possible health states are calculated using a regression model and weighted according to the social preferences of the European general population. For this population, the possible EQ-5D-3L index scores ranges from -0.11 (that is, 3 for all 5 dimensions) to 1.0 (that is, 1 for all 5 dimensions), where higher scores indicate a better health state.

End point type	Secondary

End point timeframe:

Day 30, 90 any End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	207[37]	162[38]	157[39]	158[40]
Units: Scores on scale				
arithmetic mean (standard deviation)				
Baseline (n=201, 160, 156, 157, 158,158)	0.58 (± 0.25)	0.59 (± 0.25)	0.62 (± 0.23)	0.58 (± 0.23)
Day 30 (n=173, 141,137,143,139,135)	0.06 (± 0.23)	0.02 (± 0.24)	0.02 (± 0.23)	0.07 (± 0.22)
Day 90 (n=139, 117,122,117,126,120)	0.08 (± 0.24)	0.03 (± 0.27)	0.04 (± 0.25)	0.08 (± 0.2)
Last on-treatment (n=174, 143,138,145,138,140)	0.06 (± 0.23)	0.04 (± 0.28)	0.04 (± 0.25)	0.08 (± 0.22)
Premature discontinuation (n=33,20,19,21,17,23)	-0.12 (± 0.25)	-0.06 (± 0.29)	-0.09 (± 0.24)	-0.1 (± 0.24)
Follow-up (n=161,129,136,133,144,139)	0.06 (± 0.26)	0.01 (± 0.25)	0.01 (± 0.27)	0.08 (± 0.23)

Notes:

[37] - FAS

[38] - FAS

[39] - FAS

[40] - FAS

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[41]	158[42]		
Units: Scores on scale				
arithmetic mean (standard deviation)				
Baseline (n=201, 160, 156, 157, 158,158)	0.56 (± 0.25)	0.59 (± 0.24)		
Day 30 (n=173, 141,137,143,139,135)	0.06 (± 0.23)	0.02 (± 0.25)		
Day 90 (n=139, 117,122,117,126,120)	0.1 (± 0.24)	0.06 (± 0.28)		
Last on-treatment (n=174, 143,138,145,138,140)	0.09 (± 0.24)	0.06 (± 0.28)		
Premature discontinuation (n=33,20,19,21,17,23)	-0.05 (± 0.25)	0 (± 0.29)		
Follow-up (n=161,129,136,133,144,139)	0.07 (± 0.23)	0.04 (± 0.28)		

Notes:

[41] - FAS

[42] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Serum Potassium at Specified Time Points

End point title	Change From Baseline in Serum Potassium at Specified Time Points

End point description:

Serum Potassium is a standard clinical chemistry parameter. In the below table, categorical data represents change from baseline data at respective time points.

End point type	Other pre-specified

End point timeframe:

From Baseline until the end of follow-up (30 days post dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	221	172	162	167
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Baseline (n=221,172,162,167,168,163)	4.159 (± 0.495)	4.081 (± 0.501)	4.211 (± 0.541)	4.174 (± 0.443)
Day 30 (Day 30±2) (n=178,136,137,142,143,137)	0.057 (± 0.608)	0.135 (± 0.573)	0.075 (± 0.523)	0.085 (± 0.475)

Day 60 (Day 60±2) (n=151,130,125,129,134,129)	0.179 (± 0.589)	0.091 (± 0.568)	0.131 (± 0.566)	0.171 (± 0.54)
Day 90 (Day 90±2) (n=143,117,118,121,128,119)	0.307 (± 0.609)	0.184 (± 0.574)	0.153 (± 0.516)	0.164 (± 0.579)
Last on-Treatment (n=208,164,155,162,163,156)	0.257 (± 0.647)	0.159 (± 0.585)	0.151 (± 0.562)	0.219 (± 0.628)
Follow-up (n=164,131,139,134,145,137)	0.117 (± 0.621)	0.226 (± 0.694)	0.054 (± 0.623)	0.05 (± 0.572)

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	163		
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Baseline (n=221,172,162,167,168,163)	4.131 (± 0.506)	4.117 (± 0.506)		
Day 30 (Day 30±2) (n=178,136,137,142,143,137)	0.21 (± 0.592)	0.193 (± 0.556)		
Day 60 (Day 60±2) (n=151,130,125,129,134,129)	0.274 (± 0.522)	0.216 (± 0.547)		
Day 90 (Day 90±2) (n=143,117,118,121,128,119)	0.275 (± 0.58)	0.245 (± 0.574)		
Last on-Treatment (n=208,164,155,162,163,156)	0.306 (± 0.66)	0.295 (± 0.611)		
Follow-up (n=164,131,139,134,145,137)	0.175 (± 0.559)	0.036 (± 0.556)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Blood Pressure Systolic Blood Pressure (SBP) at Specified Time Points

End point title	Change From Baseline in Blood Pressure Systolic Blood Pressure (SBP) at Specified Time Points

End point description:

Systolic blood pressure (SBP) is a directly non-invasively measured hemodynamic parameter. In the below table, categorical data represents change from baseline data at respective time points.

End point type	Other pre-specified

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	218[43]	171[44]	160[45]	165[46]
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=218,171,160,165,169,163)	120.554 (± 18.706)	119.492 (± 16.348)	118.498 (± 14.355)	119.087 (± 16.677)
Day 7 (n=204,158,154,158,163,157)	-0.541 (± 13.894)	-3.178 (± 13.72)	-2.565 (± 12.278)	0.568 (± 12.733)
Day 14 (n=49,27,40,36,37,32)	-3.442 (± 14.258)	-4.488 (± 10.31)	4.142 (± 15.001)	1.241 (± 13.561)
Day 30 (n=177,143,138,147,145,139)	0.067 (± 15.312)	-0.824 (± 15.747)	-0.367 (± 14.984)	0.374 (± 14.433)
Day 60 (n=155,128,130,129,139,131)	0.684 (± 16.315)	0.337 (± 14.176)	-1.249 (± 13.659)	-1.811 (± 14.462)
Day 90 (n=141,119,121,121,131,122)	-0.967 (± 16.408)	0.922 (± 15.847)	0.047 (± 15.643)	-0.664 (± 15.018)
Last on-Treatment (n=201,160,153,160,163,157)	-1.723 (± 16.065)	-0.33 (± 16.259)	-1.42 (± 15.469)	-0.192 (± 15.082)
Premature discontinuation (n=37,24,24,23,25,24)	-2.991 (± 16.456)	-0.41 (± 13.936)	-2.167 (± 19.963)	9.391 (± 22.378)
Follow-up (n=165,131,141,135,153,143)	0.188 (± 16.751)	2.869 (± 15.502)	1.95 (± 16.148)	-0.928 (± 17.953)

Notes:

[43] - SAF

[44] - SAF

[45] - SAF

[46] - SAF

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169[47]	163[48]		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=218,171,160,165,169,163)	116.024 (± 16.895)	116.941 (± 16.548)		
Day 7 (n=204,158,154,158,163,157)	0.162 (± 15.416)	-0.546 (± 13.498)		
Day 14 (n=49,27,40,36,37,32)	-3.099 (± 12.591)	-2.906 (± 15.406)		
Day 30 (n=177,143,138,147,145,139)	1.786 (± 15.039)	0.899 (± 14.608)		
Day 60 (n=155,128,130,129,139,131)	0.981 (± 15.525)	0.667 (± 14.83)		
Day 90 (n=141,119,121,121,131,122)	1.216 (± 17.831)	0.956 (± 15.743)		
Last on-Treatment (n=201,160,153,160,163,157)	1.072 (± 17.123)	0.516 (± 16.429)		
Premature discontinuation (n=37,24,24,23,25,24)	-2.32 (± 11.963)	-0.028 (± 15.42)		
Follow-up (n=165,131,141,135,153,143)	2.041 (± 16.189)	3.037 (± 16.782)		

Notes:

[47] - SAF

[48] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Blood Pressure Diastolic Blood Pressure (DBP) at Specified Time Points

End point title	Change From Baseline in Blood Pressure Diastolic Blood Pressure (DBP) at Specified Time Points

End point description:

Diastolic blood pressure (DBP) is a directly non-invasively measured hemodynamic parameter. In the below table, categorical data represents change from baseline data at respective time points.

End point type	Other pre-specified

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	218[49]	171[50]	160[51]	165[52]
Units: millimeter for mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=218,171,160,165,169,163)	71.633 (± 11.647)	71.044 (± 10.762)	71.442 (± 8.508)	70.61 (± 9.692)
Day 7 (n=204,158,154,158,163,157)	-1.351 (± 10.237)	-1.693 (± 9.911)	-2.143 (± 9.848)	0.013 (± 9.733)
Day 14 (n=49,27,40,36,37,32)	-3.442 (± 10.089)	-0.537 (± 9.59)	1.608 (± 9.423)	-0.083 (± 7.421)
Day 30 (n=177,143,138,147,145,139)	-0.503 (± 10.826)	0.146 (± 10.667)	-0.845 (± 8.91)	-0.068 (± 9.633)
Day 60 (n=155,128,130,129,139,131)	-0.613 (± 11.096)	-0.199 (± 11.297)	-2.144 (± 9.552)	-0.85 (± 10.472)
Day 90 (n=141,119,121,121,131,122)	-0.716 (± 11.035)	-0.106 (± 11.148)	-1.738 (± 9.015)	-1.121 (± 9.96)
Last on-Treatment (n=201,160,153,160,163,157)	-1.003 (± 10.841)	-0.466 (± 11.532)	-2.383 (± 10.064)	-0.777 (± 9.842)
Premature discontinuation (n= 36,24,24,23,25,24)	-3.185 (± 11.853)	0.868 (± 9.239)	-2.194 (± 15.522)	4.101 (± 12.151)
Follow-up (n=165,131,141,135,153,143)	-1.218 (± 11.477)	0.696 (± 13.172)	-0.444 (± 10.197)	-1.16 (± 11.114)

Notes:

[49] - SAF

[50] - SAF

[51] - SAF

[52] - SAF

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169[53]	163[54]		
Units: millimeter for mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=218,171,160,165,169,163)	70.343 (± 10.394)	71.145 (± 9.809)		
Day 7 (n=204,158,154,158,163,157)	-0.738 (± 10.534)	-1.166 (± 8.964)		
Day 14 (n=49,27,40,36,37,32)	-2.387 (± 10.51)	-0.625 (± 9.41)		
Day 30 (n=177,143,138,147,145,139)	-0.094 (± 10.086)	-1.163 (± 9.622)		
Day 60 (n=155,128,130,129,139,131)	0.17 (± 10.312)	-0.575 (± 10.427)		
Day 90 (n=141,119,121,121,131,122)	-0.545 (± 11.212)	-0.877 (± 11.327)		
Last on-Treatment (n=201,160,153,160,163,157)	-0.44 (± 10.716)	-1.121 (± 11.52)		
Premature discontinuation (n= 36,24,24,23,25,24)	-2.96 (± 9.199)	-0.083 (± 10.113)		
Follow-up (n=165,131,141,135,153,143)	-0.298 (± 11.521)	-0.172 (± 10.211)		

Notes:

[53] - SAF

[54] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in in Heart rate at Specified Time Points

End point title	Change From Baseline in in Heart rate at Specified Time Points

End point description:

Heart rate (HR) is a directly non-invasively measured hemodynamic parameter. In the below table, categorical data represents change from baseline data at respective time points.

End point type	Other pre-specified

End point timeframe:

Day 30, 60, 90, End of Treatment, End of Follow-up (30 days post-last dose)

End point values	Eplerenone (INSPRA®)	Finerenone (BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD	Finerenone (BAY94-8862) 7.5-15 mg OD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	217[55]	171[56]	160[57]	165[58]
Units: Beats per minute (Beats/min)				
arithmetic mean (standard deviation)				
Baseline (n=217,171,160,165,169,162)	74.957 (± 13.813)	73.369 (± 13.396)	72.681 (± 12.623)	74.184 (± 12.369)
Day 7 (n=203,158,153,158,163,157)	-0.8 (± 10.751)	1.073 (± 13.5)	-0.63 (± 11.696)	-0.719 (± 10.77)

Day 14 (n=49,27,40,36,37,32)	-3.109 (± 15.101)	0.599 (± 16.387)	1.842 (± 14.988)	-1.324 (± 13.666)
Day 30(n=176,143,138,147,145,139)	0.294 (± 13.61)	1.064 (± 14.128)	0.435 (± 13.63)	-0.349 (± 12.636)
Day 60 (n=155,128,130,129,139,131)	0.297 (± 13.033)	-0.975 (± 14.953)	-1.741 (± 10.86)	-2.318 (± 14.225)
Day 90 (n=141,119,121,121,131,122)	-0.189 (± 12.289)	-1.647 (± 13.001)	-2.89 (± 12.034)	-2.212 (± 12.041)
Last on-Treatment (n=201,160,153,160,163,157)	-0.216 (± 13.172)	-0.476 (± 14.516)	-2.453 (± 11.945)	-1.94 (± 11.563)
Premature discontinuation (n= 36,24,24,23,25,23)	-2.278 (± 15.909)	-1.424 (± 15.587)	-0.222 (± 7.591)	1.101 (± 10.22)
Follow-up (n=165,131,141,135,153,143)	-1.281 (± 13.789)	-2.057 (± 13.982)	-0.626 (± 14.196)	-1.326 (± 15.488)

Notes:

[55] - SAF

[56] - SAF

[57] - SAF

[58] - SAF

End point values	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169[59]	162[60]		
Units: Beats per minute (Beats/min)				
arithmetic mean (standard deviation)				
Baseline (n=217,171,160,165,169,162)	73.852 (± 11.999)	74.329 (± 13.187)		
Day 7 (n=203,158,153,158,163,157)	-0.548 (± 11.144)	-1.176 (± 13.398)		
Day 14 (n=49,27,40,36,37,32)	0.423 (± 11.247)	-3.969 (± 13.715)		
Day 30(n=176,143,138,147,145,139)	-0.802 (± 11.311)	-1.633 (± 12.719)		
Day 60 (n=155,128,130,129,139,131)	0.192 (± 13.377)	-1.608 (± 13.828)		
Day 90 (n=141,119,121,121,131,122)	-0.71 (± 13.777)	-1.145 (± 14.284)		
Last on-Treatment (n=201,160,153,160,163,157)	-0.162 (± 13.265)	-2.066 (± 15.649)		
Premature discontinuation (n= 36,24,24,23,25,23)	4.733 (± 13.646)	-2.072 (± 19.731)		
Follow-up (n=165,131,141,135,153,143)	0.834 (± 14.159)	-1.317 (± 14.636)		

Notes:

[59] - SAF

[60] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment until 3 days after last dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Eplerenone (INSPRA®)

Reporting group description:

Eplerenone 25mg capsule every other day (EOD), on Day 1, Day 3, Day 5, etc, along with placebo capsule (matched to Eplerenone capsule) on Day 2, Day 4, Day 6, etc., and placebo tablet (matched to Finerenone tablet) once daily (OD). The dose could be increased to 25 mg OD at Day 30 and to 50 mg OD at Day 60 (or 25 mg OD if no up-titration occurred on Day 30) if both up-titration steps were performed. Treatment duration was for 90 days.

Reporting group title	Finerenone(BAY94-8862) 2.5-5 mg OD

Reporting group description:

Finerenone 2.5 mg immediate-release (IR) tablets OD and placebo-matched to Eplerenone capsule OD, with possible up-titration to 5 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Reporting group title	Finerenone (BAY94-8862) 5-10 mg OD

Reporting group description:

Finerenone 5 mg IR tablets OD and placebo-matched to Eplerenone capsule OD, with possible up-titration to 10 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Reporting group title	Finerenone (BAY94-8862) 7.5-15 mg OD

Reporting group description:

Finerenone 7.5 mg IR tablet OD and placebo-matched to Eplerenone capsule OD, with possible up-titration to 15 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Reporting group title	Finerenone (BAY94-8862) 10-20 mg OD

Reporting group description:

Finerenone 10 mg IR tablet OD and placebo-matched to Eplerenone capsule OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Reporting group title	Finerenone (BAY94-8862) 15-20 mg OD

Reporting group description:

Finerenone 15 mg IR tablet OD and placebo-matched to Eplerenone capsule OD, with possible up-titration to 20 mg OD at Day 30 (Day 30±2) and sham up-titration at Day 60 (Day 60±2). Treatment duration was for 90 days.

Serious adverse events	Eplerenone (INSPRA®)	Finerenone(BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 221 (34.84%)	72 / 172 (41.86%)	47 / 163 (28.83%)
number of deaths (all causes)	19	17	9
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Deep vein thrombosis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker removal			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardioversion			
subjects affected / exposed	2 / 221 (0.90%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot amputation			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe amputation			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implantable defibrillator insertion			

subjects affected / exposed	1 / 221 (0.45%)	2 / 172 (1.16%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular assist device insertion			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac rehabilitation therapy			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac resynchronisation therapy			
subjects affected / exposed	0 / 221 (0.00%)	2 / 172 (1.16%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ablation			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth extraction			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Percutaneous coronary intervention			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			

subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 221 (0.45%)	2 / 172 (1.16%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 1
Sudden cardiac death			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Oedema due to cardiac disease			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site haematoma			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site ulcer			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choking			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 221 (0.90%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			

subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep disorder			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium increased			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Computerised tomogram abdomen abnormal			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			

subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Contusion			

subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergic transfusion reaction			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			

subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	3 / 221 (1.36%)	1 / 172 (0.58%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	21 / 221 (9.50%)	16 / 172 (9.30%)	15 / 163 (9.20%)
occurrences causally related to treatment / all	0 / 27	0 / 26	0 / 17
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 2
Cardiac failure acute			
subjects affected / exposed	6 / 221 (2.71%)	6 / 172 (3.49%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 6	1 / 6	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	13 / 221 (5.88%)	9 / 172 (5.23%)	7 / 163 (4.29%)
occurrences causally related to treatment / all	1 / 16	0 / 11	0 / 7
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 0
Cardiac failure congestive			
subjects affected / exposed	4 / 221 (1.81%)	5 / 172 (2.91%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	2 / 221 (0.90%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial haemorrhage			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			

subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	3 / 221 (1.36%)	3 / 172 (1.74%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ventricular tachycardia			
subjects affected / exposed	2 / 221 (0.90%)	4 / 172 (2.33%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachyarrhythmia			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhage intracranial			

subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 221 (0.90%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	2 / 221 (0.90%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stasis dermatitis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			

subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 221 (0.45%)	2 / 172 (1.16%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 221 (0.00%)	5 / 172 (2.91%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	1 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal failure chronic			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			

subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Erysipelas			
subjects affected / exposed	2 / 221 (0.90%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 221 (0.45%)	3 / 172 (1.74%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 221 (0.90%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			

subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis bacterial			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	5 / 221 (2.26%)	6 / 172 (3.49%)	4 / 163 (2.45%)
occurrences causally related to treatment / all	5 / 5	4 / 6	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 221 (0.45%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 221 (0.00%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 221 (0.45%)	1 / 172 (0.58%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 221 (0.00%)	0 / 172 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Finerenone (BAY94-8862) 7.5-15 mg OD	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 167 (31.14%)	46 / 169 (27.22%)	57 / 163 (34.97%)
number of deaths (all causes)	12	2	9
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			

subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			

subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 167 (0.00%)	2 / 169 (1.18%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker removal			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardioversion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot amputation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe amputation			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implantable defibrillator insertion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular assist device insertion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac rehabilitation therapy			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac resynchronisation therapy			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ablation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth extraction			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Percutaneous coronary intervention			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 167 (0.60%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			

subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema due to cardiac disease			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site haematoma			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site ulcer			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Choking			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Delirium			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep disorder			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium increased			
subjects affected / exposed	1 / 167 (0.60%)	1 / 169 (0.59%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Computerised tomogram abdomen abnormal			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Accident			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergic transfusion reaction			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 167 (0.60%)	2 / 169 (1.18%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Cardiac failure			
subjects affected / exposed	21 / 167 (12.57%)	11 / 169 (6.51%)	13 / 163 (7.98%)
occurrences causally related to treatment / all	1 / 33	0 / 12	0 / 14
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 167 (0.60%)	3 / 169 (1.78%)	5 / 163 (3.07%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	8 / 167 (4.79%)	6 / 169 (3.55%)	12 / 163 (7.36%)
occurrences causally related to treatment / all	0 / 9	0 / 6	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Cardiac failure congestive			
subjects affected / exposed	2 / 167 (1.20%)	0 / 169 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	3 / 167 (1.80%)	1 / 169 (0.59%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachyarrhythmia			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear			

subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			

subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stasis dermatitis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haematuria			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	4 / 167 (2.40%)	2 / 169 (1.18%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	1 / 4	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	2 / 167 (1.20%)	0 / 169 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 167 (0.60%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Muscle haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 167 (0.60%)	2 / 169 (1.18%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 167 (1.20%)	2 / 169 (1.18%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 167 (0.00%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	1 / 167 (0.60%)	1 / 169 (0.59%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis bacterial			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	7 / 167 (4.19%)	5 / 169 (2.96%)	6 / 163 (3.68%)
occurrences causally related to treatment / all	6 / 7	5 / 5	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 167 (0.60%)	1 / 169 (0.59%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 167 (0.00%)	2 / 169 (1.18%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			

subjects affected / exposed	0 / 167 (0.00%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 167 (0.60%)	0 / 169 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Eplerenone (INSPRA®)	Finerenone(BAY94-8862) 2.5-5 mg OD	Finerenone (BAY94-8862) 5-10 mg OD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 221 (38.46%)	63 / 172 (36.63%)	59 / 163 (36.20%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	12 / 221 (5.43%)	5 / 172 (2.91%)	7 / 163 (4.29%)
occurrences (all)	14	5	7
Vascular disorders			
Hypotension			
subjects affected / exposed	11 / 221 (4.98%)	7 / 172 (4.07%)	11 / 163 (6.75%)
occurrences (all)	13	7	12
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	13 / 221 (5.88%)	14 / 172 (8.14%)	10 / 163 (6.13%)
occurrences (all)	14	20	11
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 221 (5.43%)	8 / 172 (4.65%)	6 / 163 (3.68%)
occurrences (all)	13	8	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 221 (3.62%)	6 / 172 (3.49%)	6 / 163 (3.68%)
occurrences (all)	8	6	6
Nausea			
subjects affected / exposed	7 / 221 (3.17%)	9 / 172 (5.23%)	2 / 163 (1.23%)
occurrences (all)	7	12	2

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	11 / 221 (4.98%)	12 / 172 (6.98%)	7 / 163 (4.29%)
occurrences (all)	12	13	7
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	8 / 221 (3.62%)	6 / 172 (3.49%)	7 / 163 (4.29%)
occurrences (all)	10	8	9
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	8 / 221 (3.62%)	5 / 172 (2.91%)	7 / 163 (4.29%)
occurrences (all)	9	5	10
Hypokalaemia			
subjects affected / exposed	34 / 221 (15.38%)	20 / 172 (11.63%)	21 / 163 (12.88%)
occurrences (all)	44	26	28

Non-serious adverse events	Finerenone (BAY94-8862) 7.5-15 mg OD	Finerenone (BAY94-8862) 10-20 mg OD	Finerenone (BAY94-8862) 15-20 mg OD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 167 (29.94%)	50 / 169 (29.59%)	65 / 163 (39.88%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 167 (1.80%)	4 / 169 (2.37%)	8 / 163 (4.91%)
occurrences (all)	3	4	9
Vascular disorders			
Hypotension			
subjects affected / exposed	11 / 167 (6.59%)	7 / 169 (4.14%)	8 / 163 (4.91%)
occurrences (all)	14	7	8
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	5 / 167 (2.99%)	7 / 169 (4.14%)	10 / 163 (6.13%)
occurrences (all)	6	7	10
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 167 (3.59%)	7 / 169 (4.14%)	6 / 163 (3.68%)
occurrences (all)	6	7	7
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	10 / 167 (5.99%)	6 / 169 (3.55%)	7 / 163 (4.29%)
occurrences (all)	11	6	9
Nausea			
subjects affected / exposed	5 / 167 (2.99%)	2 / 169 (1.18%)	6 / 163 (3.68%)
occurrences (all)	7	2	6
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 167 (3.59%)	3 / 169 (1.78%)	10 / 163 (6.13%)
occurrences (all)	7	4	11
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	6 / 167 (3.59%)	8 / 169 (4.73%)	9 / 163 (5.52%)
occurrences (all)	10	11	9
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	7 / 167 (4.19%)	6 / 169 (3.55%)	9 / 163 (5.52%)
occurrences (all)	7	6	9
Hypokalaemia			
subjects affected / exposed	15 / 167 (8.98%)	14 / 169 (8.28%)	17 / 163 (10.43%)
occurrences (all)	30	18	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2014	1. The specification that potassium was to be monitored in serum was removed; potassium during the treatment period could be monitored in serum or plasma. A paragraph detailing the prohibited use of potassium lowering agents was added. 2. The inclusion criteria were modified with respect to the inclusion of women of childbearing potential. 3. A cap of 45% for subjects with atrial fibrillation was introduced. 4. Definitions of "mineralocorticoid receptor antagonist (MRA) naïve" and "previous MRA use" for stratification were added. 5. It was clarified that concomitant treatment with an angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin receptor blocker (ARB) was prohibited. Diltiazem was removed from the list of moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitory. 6. A pregnancy test was added at the screening visit for women of childbearing potential. 7. It was clarified that the latest assessed left ventricular ejection fraction (LVEF) value recorded for medical history had to be prior to the screening visit. 8. The symptom burden domain and the total symptom scale were added to the KCCQ. 9. The requirement to report adverse event (AEs) of special interest as serious adverse event (SAEs) was added. 10. An un-blinding waiver and exemption from expedited reporting requirements were introduced for specific disease related AEs. 11. The assessment schedule if the screening visit and Visit 1 (Day 1) took place on the same day was clarified. 12. The definition of the SAF was modified to all randomized subjects who took at least one dose of study drug and with data after beginning of treatment. 13. Further details were added on general statistical considerations, the analysis of the primary efficacy variable, health related quality of life, AEs, safety laboratory parameters, and safety biomarkers, and subgroup analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Occurrence of "±" in relation with geometric CV is autogenerated and cannot be deleted. Decimal places were automatically truncated if last decimal equals zero.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25678098

http://www.ncbi.nlm.nih.gov/pubmed/27130705